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Liver Adenomatosis: Reappraisal, Diagnosis, and Surgical Management

Eight New Cases and Review of the Literature

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Objective

Liver adenomatosis (LA) is a rare disease originally defined by Flejou et al in 1985 from a series of 13 cases. In 1998, 38 cases were available for analysis, including eight personal cases. The aim of this study was to review and reappraise the characteristics of this rare liver disease and to discuss diagnosis and therapeutic options.

Background

LA was defined as the presence of >10 adenomas in an otherwise normal parenchyma. Neither female predominance nor a relation with estrogen/progesterone intake has been noted. Natural progression is poorly known.

Methods

The clinical presentation, evolution, histologic characteristics, and therapeutic options and results were analyzed based on a personal series of eight new cases and an updated review of the literature.

Results

From a diagnostic standpoint, two forms of liver adenomatosis with different presentations and evolution can be defined: a massive form and a multifocal form. The role of estrogen and progesterone is reevaluated. The risks of hemorrhage and malignant transformation are of major concern. In the authors' series, liver transplantation was indicated in two young women with the massive, aggressive form, and good results were obtained.

Conclusion

Liver adenomatosis is a rare disease, more common in women, where outcome and evolution vary and are exacerbated by estrogen intake. Most often, conservative surgery is indicated. Liver transplantation is indicated only in highly symptomatic and aggressive forms of the disease.

Adenoma is a benign neoplasm of the liver occurring in young women, in whom an association with estrogen/progesterone therapy has been established.[1,2] The tumor is usually solitary, but multiple adenomas have been described, ranging from two or three nodules[3] to multiple or disseminated lesions of variable size. The latter entity is termed liver adenomatosis (LA).[4]

Despite several cases reported in the literature, LA remains a poorly understood disease of unknown etiology. Management has seldom been discussed. In 1985, Flejou et al[4] reviewed all published cases and added five cases of their own. They defined LA as the presence of ≥10 adenomas in an otherwise normal liver parenchyma, thus excluding patients with glycogen storage disease or those with a history of steroid intake. They also noticed that the male-to-female distribution was equal in LA (unlike in hepatic adenoma), that LA was not associated with oral contraceptive use, and that it had a propensity to hemorrhagic and necrotic complications. In the literature, we noted that treatment has mostly consisted of partial liver resection, but very few data are available on long-term follow-up.[5]

In this article we report eight new cases of LA. Based on these cases and an up-to-date review of the literature, the

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characteristics of LA are reappraised and the problems inherent in its diagnosis and therapeutic management are discussed.

MATERIALS AND METHODS

Between 1980 and 1998, 10 patients were referred to the University Hospital of Caen with the diagnosis of LA. In 1998, all these cases were reexamined by two experienced independent pathologists. A definite diagnosis, based on imaging findings and microscopic examination of a percutaneous biopsy ($n = 1$) or surgical liver specimen ($n = 7$), was confirmed in 8 of the 10. In all cases, a glycogen storage disease was excluded, and no patient had received prior androgenic steroid therapy. We reviewed the clinical presentation, radiologic characteristics, histopathologic findings, surgical procedures, and outcomes of those patients, paying special attention to the long-term follow-up.

RESULTS

Patient characteristics are shown in Table 1. The male: female ratio was 1:7. The mean age at diagnosis was 32 (range 14–45) years. Among the seven women, three had been taking estrogen/progesterone therapy for 1, 6, and 15 years. Four patients (patients 1–4) in this short series belonged to the same family and had insulin-dependent diabetes with hypertension. Two patients had mental deficiency due to congenital toxoplasmosis.

In two patients, the disease was revealed by intraperitoneal bleeding. One died before laparotomy and the diagnosis was made at necropsy (Fig. 1); the other underwent urgent surgery. Three patients were admitted for acute abdominal pain corresponding to intratumoral bleeding or necrosis of one of the adenomas. In one patient, the diagnosis of abscess had been made elsewhere. The last three patients were asymptomatic.

Diagnosis

Laboratory studies revealed nonspecific signs, depending on the presentation. A two- or threefold increase in serum aminotransferase was observed in necrosis of one adenoma. Otherwise, the biologic workup was normal or showed a two- or three-fold increase of alkaline phosphatase or gamma glutamyl transpeptidase levels.

The extent of radiologic investigation depended on that patient's presentation. One patient had no radiologic investigation because she arrived at the hospital in cardiac arrest from massive bleeding. Four patients had a symptomatic or complicated liver tumor that required urgent laparotomy, so that only sonography and computed tomography (CT) were performed. The three other patients also underwent magnetic resonance imaging (MRI).

In patients with symptomatic or complicated adenomas (hemorrhage, necrosis, or rupture), sonography showed a huge, heterogeneous tumor measuring 6 to 12 cm with a fluid component corresponding to necrosis or hemorrhage, surrounded by several nodules of different sizes and different behavior patterns, depending on their size. CT with enhancement favored the diagnosis of a vascularized tumor with hemorrhage, but the other tumors were hardly seen.

In asymptomatic or poorly symptomatic forms of the disease, sonography demonstrated multiple hyperechoic nodules in the liver measuring 4 cm to <1 cm. CT with enhancement showed the lesions to be hypodense, contrasting with the usual behavior of adenomas. The abnormalities were not visible on regular spin-echo T1- and T2-weighted MRI scans, but multiple hyperintense nodules were highlighted on ultrafast echo-gradient sequences after gadolinium bolus injection (FMSGPR).

Laparotomy (or in one case necropsy) revealed two types of LA. In four patients, the liver was enlarged and its contour was deformed by multiple, bulging, rounded, yellow nodules measuring 2 to 10 cm. In this type, which will be called the massive form, nodules were innumerable, several being 3 or 4 cm or more. In three patients, the liver was not enlarged. Multiple yellow nodules <1 cm were observed but were hardly palpable. Few were >4 cm. This form will be called multifocal.

Diagnosis was made by histology of the surgical specimen seven times, once by percutaneous biopsy. One of the asymptomatic patients underwent two percutaneous biopsies that failed to provide the diagnosis; this patient underwent laparotomy revealing multifocal LA. Histologic data were similar in all cases, showing numerous nodules of different sizes, with several presenting hemorrhagic components (Fig. 2). Microscopic examination revealed benign hepatocytes arranged in thickened cords. Steatosis was always present to variable degrees. Some nodules were encapsulated (the larger); others were not. Portal tracts and bile ducts were absent.

Management and Outcome

One 18-year-old noninsulin-dependent diabetic woman, treated for hypertension with beta blockers, had violent right upper quadrant pain at home, went into cardiac arrest, and could not be resuscitated. At necropsy (see Fig. 1), death was found to be due to rupture of a huge adenoma in a massive form of LA. The liver weighed 4,200 g. Diagnosis was made by laparotomy in six of the remaining seven patients; the other patient had a positive percutaneous liver biopsy. In two cases laparotomy was performed for diagnosis of multinodular liver. Four patients underwent emergency surgery for complications (intratumoral bleeding or necrosis) associated with intraperitoneal rupture in one and in another with infection, presenting as calcified liver abscess. This latter patient had mental deficiency due to congenital toxoplasmosis with agenesis of the portal trunk and focal nodular hyperplasia in the liver parenchyma.

The two last patients had a huge tumor in the right lobe

Table 1. PERSONAL SERIES: CLINICAL PRESENTATION, DIAGNOSIS, SURGICAL PROCEDURES, AND OUTCOME

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age	18	14	45	17	22	42	22	41
Sex	F	M	F	F	F	F	F	F
OC use	1 year	—	No	No	No	15 years	No	2 years
Clinical manifestation	Intraperitoneal bleeding	None	None	Pain, hepatomegaly	Pain, hepatomegaly	Intraperitoneal bleeding	Pain	Pain, weight loss
Complications	Extratumoral bleeding	None	None	Intratumoral bleeding	Intratumoral bleeding	Intraperitoneal rupture	Intratumoral necrosis	None
PA	ND	n	n	2n	2n	5n	2n	n
GGT	ND	n	n	3n	n	2n	2n	n
Sonography	ND	Hyperechoic	Hyperechoic	Hyperechoic	Heterogeneous	Hypo- and hyperechoic	Hypoechoic	Hyperechoic
CT scan	ND	Hypodense	Hypodense	Heterogeneous	Hypo- and Hyperdense	ND	Hypodense	Hypodense
MRI	ND	Hypo T1	Hypo T1	ND	Hypo T1 Hyper T2	ND	ND	Hypo T1 Hyper T2
Means of diagnosis	Necropsy	Laparotomy	Laparotomy	Laparotomy	Laparotomy	Laparotomy	Laparotomy	Biopsy
Max. size adenoma	10 cm	4 cm	4 cm	10 cm	10 cm	5 cm	6 cm	4 cm
Macroscopy	Massive	Multifocal	Multifocal	Massive	Massive	Multifocal	Massive	Multifocal
Treatment	—	Surgical biopsy	—	Liver transplantation	Liver transplantation	Left lobectomy	Right hepatectomy	None
Histologic characteristics	Steatosis	Steatosis	Steatosis	Steatosis	Steatosis, FNH	Steatosis	FNH	Steatosis
Outcome	Dead	Alive 1 year, stable	Alive 9 years, progression	Alive 16 years, progression	Alive 4 years, progression	Alive 3 years, regression	Alive 6 years, progression	Alive 3 years, stable

OC, oral contraceptive; ND, not done; n, normal; FNH, focal nodular hyperplasia.

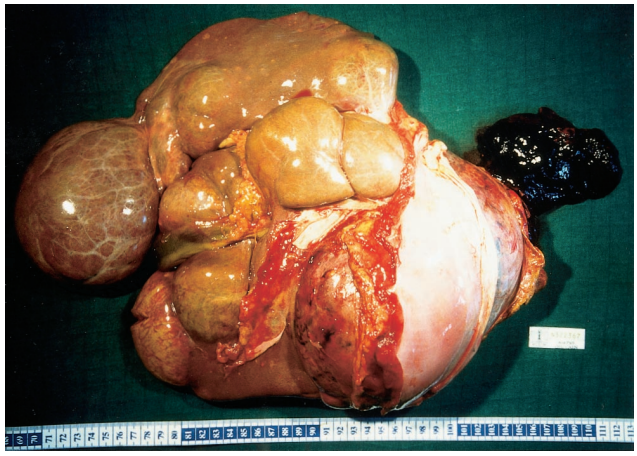

Figure 1. Necropsis: liver specimen weighing 4,200 g. The liver is deformed by huge nodules. On the right, rupture of one adenoma was responsible for intraperitoneal hemorrhage and death.

complicated by symptomatic necrosis. One underwent a posterior segmentectomy and the other underwent surgical exploration, but because there was no active intraperitoneal hemorrhage, the surgeon considered resection of the main nodule to be too dangerous. He removed a small nodule of 1.7 cm in segment 3 and took a biopsy sample from another nodule in the right lobe. Histology revealed focal nodular hyperplasia in the first specimen and necrosis in the second, with no sign of malignancy. Because of the widespread findings at exploration, a diagnosis of multiple focal hyperplasia was made. These two patients ultimately underwent transplantation because they had the aggressive form of the disease.

In follow-up, different patterns were observed. Two patients had no disease progression on imaging follow-up (1 and 3 years). One patient who was taking estrogen/progesterone at the time of diagnosis terminated her hormonal therapy, and after 3 years of follow-up and three repeat CT scans, the remaining nodules have shrunk. The patient remains asymptomatic at the time of writing. The remaining patients had progressive disease: two remained asymptomatic but had an increase in the number of lesions on sonography (follow-up 6 and 9 years).

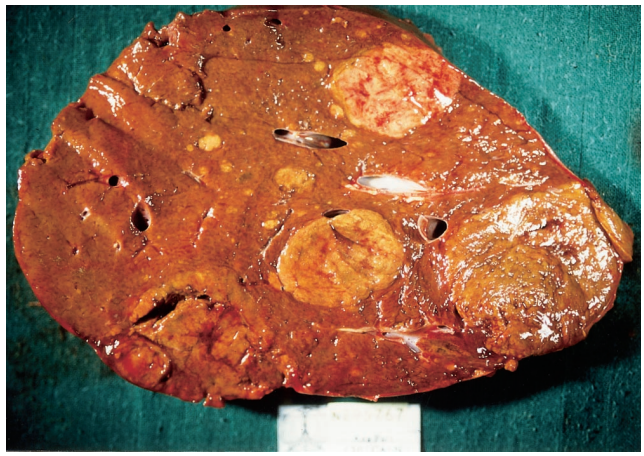

Figure 2. Macroscopic view of liver adenomatosis. Note the nodules of different size with hemorrhagic areas.

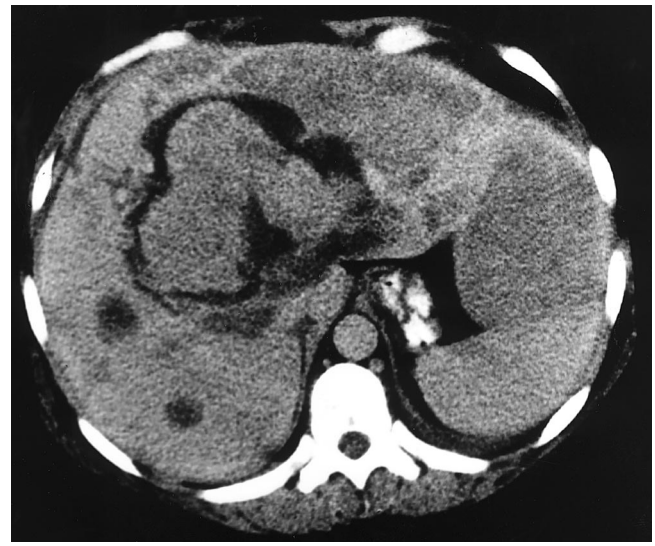

Figure 3. Computed tomography scan showing the central adenoma with intratumoral hemorrhage and another large subcapsular nodule in the left lobe.

Two patients were highly symptomatic. The first one (patient 4), who had a posterior segmentectomy in July 1980, on follow-up was found to have chronic pain associated with an increase in the number and size of the remaining nodules. The patient was depressed and had difficulty with her professional life because of absence from work due to frequent intermittent pain and asthenia. In September 1994, at age 31, she was admitted to the emergency department for an intratumoral hemorrhage of a huge central adenoma (Fig. 3). Considering the location of the main complicated nodule, the previous surgery, and the impact of the disease on her daily life, a liver transplant was performed 10 months later. The removed organ weighed 3,800 g. Innumerable adenomas were present in the parenchyma, and three had areas of ischemic necrosis or hemorrhage (see Fig. 2). No dysplastic cells were seen. Steatosis was prominent, in a variable amount from one nodule to another. The patient had an uneventful recovery and was discharged from the hospital on day 15 after the transplant. She returned to work and remains well 3 years after the transplant.

The other patient (patient 5) for whom the diagnosis of multiple local hyperplasia had been made was discharged after laparotomy and was referred to us 3 years later because the nodules were growing and the patient was having intermittent periods of acute pain. One year later, one of the main nodules had enlarged, with signs of intratumoral hemorrhage; the other nodules appeared more numerous and larger than on the initial sonogram. The diagnosis was reevaluated. Transcutaneous biopsy showed hepatocyte proliferation with some pseudoacinar arrangements (Fig. 4). A

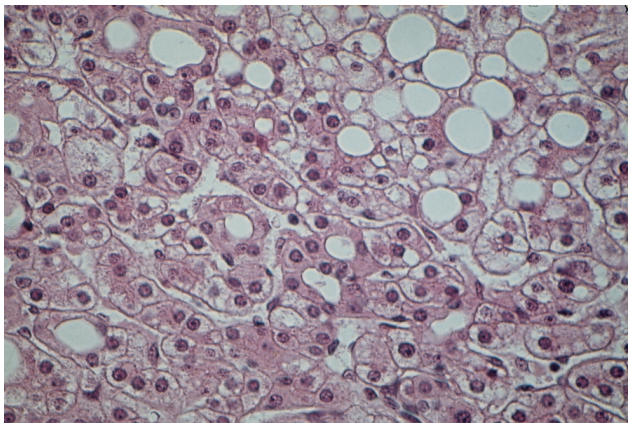

Figure 4. Pseudoacinar arrangement of hepatocytes made us suspect degeneration.

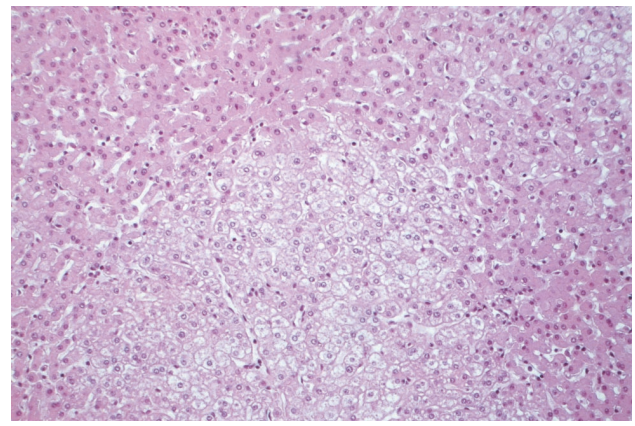

Figure 6. Adenomatous hyperplasia. The cells can be distinguished by lighter cytoplasm. Hematoxylin and eosin ×40.

diagnosis of adenoma in preference to well-differentiated carcinoma was tentatively made. The patient continued to have chronic pain with impairment of her professional and social life. She wanted to have a child, but we were worried about the evolution of such adenomas during pregnancy. Eight months after the last laparotomy, a new episode of spontaneous intratumoral hemorrhage led us to evaluate the patient for liver transplantation. The removed organ weighed 2,850 g, and its contour was deformed by multiple bulging rounded nodules measuring 2 to 7 cm, with areas of hemorrhage in the largest nodules. Microscopic examination again confirmed LA; no sign of dysplasia was identified. Three years after the transplant, the patient is alive, healthy, and well.

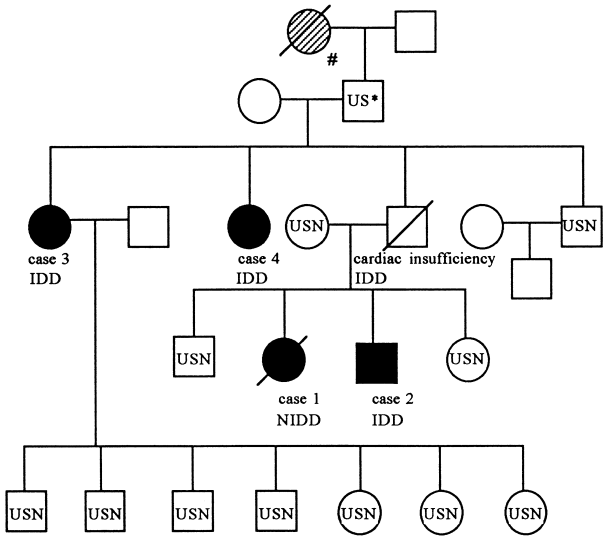

Figure 5. Genealogic tree of patients 1 to 4. Circles or boxes with a slash indicate that that person is dead; #, hepatic hemorrhage after minimal trauma (further data not available); US*, one hyperechoic nodule detected on ultrasound; USN, ultrasound considered normal; IDD, insulin-dependent diabetes; NIDD, noninsulin-dependent diabetes.

DISCUSSION

When added to the 30 previous cases collected to date (Table 2), our relatively large series (eight patients) can increase our knowledge of this rare disease. Diagnosis was made at a mean of 32 years (range 13–75), in most cases because of complicated disease, as noted by Flejou et al.[4] However, from the current series and the review of the literature, several epidemiologic notions must be revised. First, in terms of the sex ratio of the disease, if we add our 7 female and 1 male patients to the 30 previously published cases, we find that LA has been described in 28 female and 10 male patients, suggesting a clear female preponderance (74%). These data are at odds with the initial definition of the disease by Flejou et al.[4]

Oral contraceptive therapy is not as rarely associated with this liver disease as initially suspected (46% of female patients). In the literature, eight patients became symptomatic because of intraperitoneal bleeding, and seven of these patients were taking contraceptives.[4,6–10] Long-term use of oral contraceptives[6,8,11] was found in several previous patients. Adenomas regressed after discontinuing hormonal contraceptive intake in patient 6. These data suggest that oral contraceptives have a role at least in the evolution of some forms of LA.

The etiology of this disease remains unknown. Some reports refer to a vascular liver problem due to altered hepatic parenchyma, intrahepatic vascular shunts, or an association with focal nodular hyperplasia.[12–14] In our series, one patient had congenital portal aplasia and two had an association with focal nodular hyperplasia, but these correlative findings are far from being the rule in the cases reported to date. The occurrence of four cases of this rare disease in four members of the same family is particularly interesting. The genealogy (Fig. 5) suggests an autosomal transmission for this disease. Diabetes was also associated with all cases, but the form of diabetes was not the same in all, and this association may be fortuitous. Still, a report by Foster et al[15] refers to a similar association in a family with

Table 2. DATA OF THE 30 CASES REPORTED IN THE LITERATURE

Author	Age	Sex	OC Use	Clinical Manifestations	Complications	Diagnosis	Macroscopy	Treatment	Histology	Outcome
Monges, 1963	56	M	No	Pain, hepatomegaly		Laparotomy	Massive, unilateral	Left hepatectomy		Unknown
Monaco, 1964	21	F	No	Pain, hepatomegaly		Laparotomy	Massive, unilateral	Right lobectomy	Steatosis	Alive, 10 months
Bisson, 1974	24	F	18 mo	Intraperitoneal bleeding	Intraperitoneal rupture	Laparotomy	Massive, unilateral	Right hepatectomy	Steatosis	Unknown
Bertrand, 1975	39	F	5 yrs	Intraperitoneal bleeding	Intraperitoneal rupture	Laparotomy	Massive, bilateral	Left lobectomy	Steatosis	Unknown
Brander, 1976	24	F	5 yrs	Intraperitoneal bleeding	Intraperitoneal rupture	Necropsy	Massive, bilateral			Dead (hemorrhage)
Caquet, 1976	44	M	No	Pain		Laparotomy	Massive, unilateral	Ligation hepatic artery		Alive, 6 months
Lui, 1980	39	F	No	Pain	Intratumoral bleeding	Necropsy	Massive, bilateral		Steatosis	Dead (embolism)
Chen, 1983	13	F	No	Hepatomegaly		Laparotomy	Multifocal		Assoc. FNH	Dead, 15 years
Flejou, 1985	31	M	No	Pain, hepatomegaly		Laparotomy	Massive bilateral	Left lobectomy		Alive, 11 months
	13	M	No	Intraperitoneal bleeding	Intraperitoneal rupture	Laparotomy	Massive bilateral			Alive, 34 months
	75	M	No	Pain, pruritus		Laparotomy	Massive bilateral			Alive, 7 months
	45	F	No	Intraperitoneal bleeding	Intraperitoneal rupture	Laparotomy	Massive bilateral			Alive, 28 months
	38	F	No	Pain, hepatomegaly		Laparotomy	Massive bilateral	Left lobectomy		Alive, 15 months
Leese, 1988	45	F	No	Pain	Intratumoral bleeding	Laparotomy	Massive bilateral	Segmentectomy		Alive
	16	M	No	Malignant transformation	Cancer	Laparotomy	Massive bilateral	Liver transplantation		Alive, 5 years
Brophy, 1989	31	F	No	Incidental		Laparotomy	Massive bilateral	Left lobectomy	Steatosis	Alive, 12 months
Leborgne, 1990	36	F	3 wks	Intraperitoneal bleeding	Intraperitoneal rupture	Laparotomy	Massive bilateral	Segmentectomy		
Choi, 1991	25	M	No	Pain		Laparoscopy	Multifocal			
Khan, 1992	30	M	No	Intraperitoneal bleeding	Intraperitoneal rupture	Laparotomy	Massive bilateral	Left lobectomy		Alive, 36 months
Lebail, 1992	39	F	18 yrs	Incidental		Laparotomy	Massive?	Right hepatectomy	Steatosis GH	Alive, 4 years
	52	F	12 yrs	Incidental		Laparotomy	Multifocal	Segmentectomy	Steatosis GH	Alive, 26 months
Kawakatsu, 1994	13	M	No	Pain, jaundice	Intratumoral bleeding	Laparotomy	Multifocal	Wedge resection	Assoc. FNH	Alive
Propst, 1995	30	F	No	Incidental	Intratumoral bleeding	Laparoscopy	Massive bilateral		Steatosis	Alive, 11 years
Arsenault, 1996	40	F	No	Pain	Intratumoral bleeding	Bilateralopsy	Multifocal		Steatosis	
Gokhale, 1996	17	F	No	Pain		Laparotomy	Multifocal		Steatosis	Alive, 1 year
Oberti, 1997	32	F	No	Weight loss		Laparotomy	Massive			Alive, 4 years
Barcet, 1996	42	F	15 yrs	Pain	Intratumoral bleeding	Laparotomy	Massive	Right hepatectomy		Alive
	36	F	6 yrs	Pain		Laparotomy	Massive			Alive
	32	F	Yes	Pain		Laparotomy	Massive	Right lobectomy		Alive
	44	F	3 yrs	Vomiting		Laparotomy	Massive	Left hepatectomy		Alive

OC, oral contraceptive; GH, granulomatous hepatitis; FNH, focal nodular hyperplasia.

diabetes and solitary or multiple adenomas. Moreover, the association of adenoma with glucose metabolism diseases such as glycogenosis is well documented. Nevertheless, our report is the first published of liver adenomatosis and diabetes. Further genetic exploration could help us understand the etiology of this complex disease, and we suggest that

familial investigations be recommended whenever a case is diagnosed.

In the literature, the diagnosis of LA was made because of complications of adenomas (intraperitoneal bleeding[4,6–10] [7 cases], intratumoral hemorrhage or necrosis producing acute pain[3,12,16–18]), because of hepatomegaly with or without symptoms,[4,19] or as an incidental discovery.[11,17] Only one report refers to malignant transformation of adenomas.[16] In our experience, the diagnosis was made because of complications in one adenoma, and in one patient the initial complication was fatal. This shows that even if the disease is benign, the risk of hemorrhage remains a major concern.

The diagnosis should be easy when laparotomy is mandatory because of intraperitoneal hemorrhage. The surgeon must resect the bleeding tumor and identify and take a biopsy of the other nodules. Diagnosis is more difficult if an emergency laparotomy is not required.

Because of a mixed distribution of tissue components in the adenomatous tumors, with frequently noted fatty infiltration and necrosis (occasionally focal and asymptomatic), and also because of their vascularity, these tumors have extremely variable characteristics. Thus, they may appear iso-, hypo-, or hyperechoic on sonography and iso-, hypo-, or hyperdense on CT. At this step of the investigation, several diagnosis may be suspected: other benign tumors or abnormalities, such as multiple focal nodular hyperplasia, multiple angioma, or focal steatosis, or malignant disease such as carcinoid tumors, rare metastatic lesions, or hepatocellular carcinoma. In LA, tumors are hypervascularized (of the arterial type) on Doppler echo and on CT and MRI after intravenous enhancement injection. In our experience, the presence of hyperechoic small nodules on ultrasound and the characteristics of the lesions on MRI are the best clues for diagnosis.[20] CT has frequently been disappointing; MRI has provided more information on the nature and the number of lesions (by using ultrafast MRI echogradient sequences with breath-holding as well as dynamic bolus enhancement by intravenous gadolinium). MRI easily excludes angiomas and steatosis, and does not find the usual signs of focal nodular hyperplasia. The combination of sonography and MRI seems the most logical diagnostic approach in this context.

All these investigations are nonspecific and do not accurately record the nature and the number of the lesions. Histology is mandatory. The histologic features are absence of cellular atypia (to differentiate from adenocarcinoma), absence of portal tracts (to differentiate from regeneration), and absence of neoductules and fibrosis (to differentiate from focal nodular hyperplasia). The diagnosis of adenoma may be difficult on a small specimen, as well as the interpretation of cellular atypia. Some degree of dysplasia may be present in adenomas (pseudofollicular pattern, as in patient 5), but this does not necessarily mean malignancy. However, malignant transformation may be focal in an adenoma,[20] and the study of a unique small specimen does not seem to provide reassurance. Besides, when large specimens are available for study, the most striking feature is the presence, between usual large adenomas, of numerous small areas of hepatocytic proliferation. These areas are the size of one or two lobules. They can be distinguished from adjacent parenchyma by a slight difference in color due to a smaller size of the cells, a lighter cytoplasm (Fig. 6), frequently with fatty infiltration at the periphery, and an arterialization of the sinusoids, which can be demonstrated by CD34 immunopositivity. These small areas of proliferation could be called "adenomatous hyperplasia." They have been detected in all our patients. Thus, the histologic hallmark of LA seems to be an adenomatous hyperplasia of the whole liver leading, eventually, to the individualization of adenomas of different size.

Thus, to make the diagnosis of LA, we prefer exploration of the liver by laparoscopy[20] or laparotomy, for several reasons. Laparotomy allows visual exploration of the liver, detecting more lesions than suspected. It also allows the surgeon to obtain biopsy specimens of several different lesions without the risk of hemorrhage: taking large specimens with macroscopically "normal" liver is the only way to observe this "adenomatous hyperplasia."

Once the diagnosis is made, management remains problematic. The main concern is the evolution of the liver disease. All the known complications of hepatic adenoma can occur in LA and are chiefly linked to the size of the tumors. Simultaneous hemorrhage in several adenomas is possible, as is recurrence of complications in different adenomas over an interval of several years (patient 4).

Our experience and a review of the literature led to the identification of two forms. The massive form, predominant in the literature, can be unilobar[6,21–23]; in those cases, the surgical option is obvious. However, more often the whole liver is enlarged and the parenchyma is tumoral and hypervascularized, making surgical management more difficult. In the multifocal form, where the liver is not enlarged, one or two of the adenomas may be larger and produce complications, but this latter presentation seems to be less progressive, and its management is easier for the surgeon.

In both forms, estrogen/progesterone therapy should be avoided to prevent complications such as rupture. The influence of pregnancy remains unknown, but we were worried about this in our second patient. In hepatic adenoma, the possibility of complications such as intratumoral hemorrhage or necrosis, of intraperitoneal rupture, or rarely of malignant transformation leads us to recommend surgical resection when the lesion is diagnosed. Of course, this cannot be applied to liver adenomatosis.

In the multifocal form of LA, surgery of the largest or of the complicated adenomas is logical. Nevertheless, we wonder whether the resection and the ensuing liver regeneration affect the evolution of the disease. Patient 4 had a dramatic progression after bisegmentectomy, in a form of LA initially judged to be multifocal but that later became a complicated massive form. In the case presented by Leese et al,[16] the young patient who showed malignant transforma-

tion had undergone a lobectomy several years previously. Liver surgery on normal parenchyma carries a low risk of morbidity, especially in specialized centers, but in the massive forms of LA it can be more difficult, especially if incident complications occur or if the complicated adenoma to be resected is central (patient 4).

The last point to be discussed is the risk of malignant transformation. An alpha-fetoprotein level assessment is recommended, but no evidence of its effectiveness is available. Only one case has been published in which the patient required liver transplantation because of degenerated adenomas.[16] In this sole case of degeneration (5 years after the initial diagnosis), alpha-fetoprotein levels were high. This indication for liver transplantation is irrefutable. Should we recommend transplantation because of the risk of degeneration? Analysis of the literature to date does not support such a recommendation. Two patients with long-term follow-up (11 and 15 years)[13,17] have not had malignant transformation. In our series, no malignant transformation was observed, despite a long follow-up (three patients with 6, 9, and 16 years of follow-up respectively). Cases of malignant transformation in solitary adenoma are also rare in the literature[24]; the one case of degeneration in 30 cases of LA in the literature is anecdotal but cannot be dismissed. The true risk is impossible to evaluate in such a rare disease, but our data do not support the concept of LA as a precancerous disease justifying preventive liver transplantation. If assurance of malignant transformation is indeed an indication for transplantation, some other indications must be present, such as in highly symptomatic massive forms with serious complications or in liver disease impairing socioprofessional day-to-day life in young patients, particularly young women trying to become pregnant. Our patients 4 and 5 clearly fall into this category. The first patient in our report also shows the risk of progression of some massive forms with large nodules in young patients. Even so, most patients with LA, particularly the multifocal form, can be managed conservatively.[11,12] Surgery is needed for acute complications, for diagnosis, and for resection of the largest adenoma as a preventive measure, as Brophy et al concluded.[25] Close follow-up is mandatory to evaluate progression.

More data are needed for the continuing evaluation of this rare liver disease and of the variants of its progression. A French registry, collecting all the national cases of the disease, is in process. Management of LA remains difficult because there is no predictive sign of its potential complications, other than the size of the adenomas. Liver resection, when necessary and possible, is the preferred option because LA is essentially a benign disease that does not impair hepatocellular function. Liver transplantation remains a difficult decision, although it is sometimes the last option, in progressive forms.

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